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Letter to the Editor

Familial Exudative Vitreoretinopathy: Further Evidence for Genetic Heterogeneity

To the Editor:

Familial exudative vitreoretinopathy (FEVR), a disorder first reported by Criswick and Schepens [1969], affects the retina and the vitreous body and is characterized by an abnormal vascularization of the peripheral retina. It is usually bilateral and often symmetric. The condition may progress to an exudative process leading to macular traction, retinal folding, and detachment. The disorder has a high degree of penetrance, and the severity is highly variable. Minimally affected patients do not show any visual symptoms, and FEVR is difficult to diagnose by clinical means alone. The manifestations are similar to retinopathy of prematurity (ROP), but the affected individuals do not have a history of oxygen therapy or low birthweight and have a normal gestational history.

FEVR usually is an autosomal dominant trait [Van Nouhuys, 1982], one form of which was mapped to 11q13 [Li et al., 1992]. However, we [Plager et al., 1992; Shastry et al., 1995] and others [Clement et al., 1995; Fullwood et al., 1993] have reported an X-linked form, suggesting heterogeneity. Many of the pathological changes associated with FEVR are very similar to Norrie disease, which is characterized by a bilateral retrolental ocular mass due to retinal dysplasia, progressive mental deterioration, and auditory impairment [Warburg 1971]. In contrast to FEVR, bilateral blindness is typically observed at birth. DNA linkage analysis has mapped the Norrie disease gene to Xp11.3-p11.2, and a candidate gene has been isolated by positional cloning. Molecular genetic analyses have shown that X-linked FEVR is allelic to the Norrie disease [Chen et al., 1993; Shastry et al., 1995; Fuchs et al., 1995]. Here we describe for the first time what appears to be autosomal recessive inheritance of FEVR.

The family shown in Figure 1 is part of an inbred Amish community and comprises 38 members with at least four consanguineous marriages (between cousins). The two affected sisters in generation IV were born at 40 weeks of gestation with normal birthweight. A detailed ophthalmological examination was performed on the two affected sisters at the age of 3 years; they were found to manifest all of the characteristics of FEVR. Ophthalmoscopy showed large retinal folds (Fig. 2C) and peripheral traction and exudates (Fig. 2D) in addition to an avascular demarcation line near the equator and vitreous detachment. The affected individuals in the third generation have similar problems. Their visual acuity ranges from 20/30 to 20/40. Available relatives were also examined (including parents) but do not seem to have any visual problems (Fig. 2A,B). A diagnosis of FEVR was established on the basis of characteristic fundus findings in the individuals lacking a history of mental or auditory impairments, premature birth, low birthweight, and exposure to supplemental oxygen. The pedigree was based on questionnaires, interviews, and ophthalmological examinations and appears to demonstrate autosomal recessive inheritance.

To categorize this family and to test the notion that autosomal dominant and recessive disorders may be linked to the same region, we have performed a haplotype analysis using the microsatellite probes that are linked to the autosomal dominant disorder [Li et al., 1992] and X-linked form [Shastry et al., 1995]. Our results indicate that the alleles of the microsatellite markers did not segregate with FEVR in this family with these markers (data not shown). In addition, when the Norrie disease gene is screened for the most popular mutation, no sequence alteration has been detected. These findings effectively rule out the 11q13 and Xp11.3 regions as candidate loci in this family that

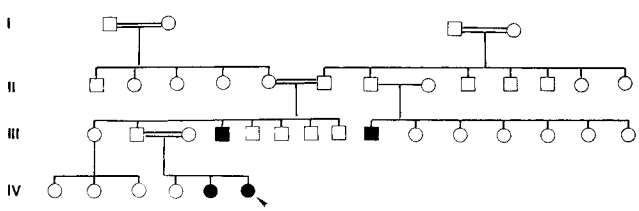

Fig. 1. Pedigree of a family with autosomal recessive FEVR. Affected and unaffected individuals are indicated by closed circles (female), closed squares (male) and open circles and squares, respectively. The family shows at least 4 consanguineous marriages. The arrow shows the proband.

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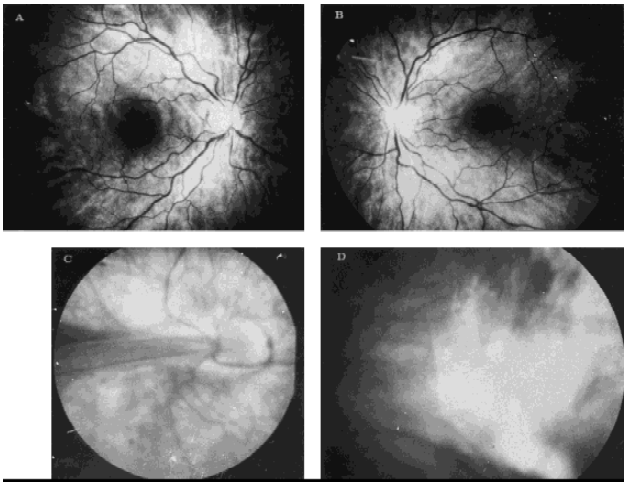

Fig. 2. Fundus picture of the right (**A**) and left eye (**B**) of the normal father of the proband. The right (**C**) and left eye (**D**) of the proband show retinal fold and exudates respectively. A similar pattern was observed with the other affected individuals.

dominant and X-linked FEVR maps. Further linkage analyses are in progress. The existence of at least two different loci for autosomal FEVR provide further evidence of heterogeneity. Knowledge that an autosomal recessive mode of transmission exists may further improve genetic counseling and diagnosis.

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